Bicuspid aortic valve associated aortopathy: a genetic disease

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Abstract

As the most common congenital heart defect, understanding the etiology and progression of aortopathy in bicuspid aortic valve (BAV) is imperative to management of patients with BAV. A reasonable hypothesis, based on the strength of evidence for both genetic and hemodynamic causes of BAV-associated thoracic aortic disease (TAD), is that BAV is caused by genetic variant(s) that also predispose to TAD by a common mechanism; presumably by cell-signaling resulting in an embryologic defect that causes BAV and a postnatal risk of TAD that is accentuated by hemodynamic stress of abnormal flow through the BAV valve. Clinical heterogeneity seen in BAV-associated TAD is likely due to individual genetic variation and the severity of hemodynamic alteration.

Introduction

Controversy exists in the literature regarding the cause(s) of bicuspid aortic valve-associated thoracic aortic disease (TAD); specifically whether it is hemodynamic in origin, or whether there are genetic causes that predispose to TAD in patients with bicuspid aortic valve (BAV). The increased aortic wall stress of chronic hypertension, smoking and age-related changes in aortic wall biology are risk factors for TAD and its morbidity and mortality.[1,2] Similarly, the long-known relationship between aortic stenosis and post-stenotic dilation of the thoracic aorta further emphasizes the importance of aortic wall stress upon development of TAD. However, it is clear that TAD is an inherited disease that occurs without apparent hemodynamic etiology.[3,4] BAV is associated with an order of magnitude increase in the lifetime prevalence of TAD to ~50%,[5] most commonly presenting as asymmetric dilation of the ascending aorta beyond the sinotubular junction, and a far-greater relative risk in younger age groups.[6] Yet not all patients with BAV will develop TAD, regardless of the severity of valve dysfunction.

The important unanswered questions surrounding TAD occurring in BAV disease are: are there specific mechanisms of TAD that occur only from the hemodynamic consequences of abnormal flow and aortic wall stress from a *normally functioning* bicuspid valve, and are there specific mechanisms for TAD that arise from genetic variation that either caused the bicuspid valve or are independent of the etiology of the bicuspid valve. These questions are important to the management of patients with BAV, notably for directing research for prevention or delaying the onset of TAD; to determine monitoring of TAD by either imaging or biomarker measurements; and for surgical management of the dilating aorta.

The aortic valve and aorta have common ectodermal and mesodermal origins

The aortic valve and aorta have common progenitor origins that underscore their propensity for concurrent congenital disease. Key molecular signaling pathways are responsible for proliferation and migration of contributing cell populations and genetic and epigenetic variation in these signaling pathways contribute to congenital heart defects.

The embryonic heart initially forms as a linear tube from first heart field progenitor cells with the primordial ventricle emptying into a single outflow tract (OFT) - the truncus arteriosus. The OFT, aortic valve and ascending aorta are formed from two populations of interdependent cells from: i) second heart field (SHF) progenitor cells arising from a pharyngeal mesodermal clonal population that also contributes to the right ventricle; ii) cardiac neural crest (CNC) cells arising from somites 1-3 of the dorsal neural crest that migrate through the pharyngeal arches into the aorta and distal OFT. The OFT is elongated during the fifth week of gestation by migrating SHF cells, forming bulbar ridges.

CNC cells contribute to the outflow tracts, aortic and pulmonary valves and the smooth muscle and connective tissue of the aorta, from the ascending aorta to the site of aortic coarctation. CNCs migrate into the bulbar ridges to form the helical aortic-pulmonary septum that fuses during the sixth gestational week, allowing for separation of the aorta and pulmonary trunk. CNCs orchestrate aortic and pulmonary valve development by CNC invasion of the endothelial cells of the primitive endocardial cushions to form recognizable thin aortic valve leaflets.[7,8] Despite considerable contribution of the CNC to the maturation of the endocardial cushions into semi-lunar valves, few CNC-derived cells are recognizable in the mature semilunar valve leaflets.[9] More likely, CNC cells drive SHF matrix production and subsequent apoptosis.[10] An example is association between *NOTCH1* mutations and BAV.[11] Notch signaling regulates endothelial-mesenchymal transformation during endocardial cushion formation,[12] perhaps by regulation of Fgf8 signaling.[13] Deficiencies in Fgf8 can cause BAV and aortic smooth muscle abnormalities.[14] The commonality of CNC in aortic valve and aortic development readily leads to the hypothesis that abnormalities of CNC proliferation, migration or signaling are responsible for the spectrum of BAV and TAD.

Bicuspid aortic valve is a polygenic abnormality

BAV is the most common congenital valvular abnormality, occurring in 0.5-1.2% of the population, more commonly in males and those with Turner syndrome,[15] and leads to greater morbidity and mortality than all other congenital heart defects combined.[16] BAV is an inherited disorder with ~9% prevalence in first-degree relatives but a variable inheritance pattern.[15,17,18] The difficulty in dissecting out the genetic causes of BAV, that may or may not also cause TAD, is because highly-penetrant single-gene inheritance is observed in only a few well-reported families.[11] Far more commonly, the inheritance pattern is unclear with few individuals in a family exhibiting BAV or TAD, indicating polygenic disease perhaps with a cumulative burden of lower-risk common and

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uncommon variants in the etiology of BAV. To date, rare variants or haploinsufficiency of *NOTCH1*, *GATA4/5/6*, *NOS3* and other genes have been associated with BAV in mice and humans. These genes have key signaling roles in both SHF and CNC migration and cell-signaling and are likely causative of BAV.[11,19-24]

Thoracic aortic disease is a polygenic disease

An increasing list of common and uncommon genetic variants have been demonstrated to be associated with TAD, including common variants in *FBN1*,[25] and uncommon or rare variants in *ACTA2*, *FBN1*, *FLNA*, *MYH11*, *SMAD3* and *TGFBR1/2*, amongst others.[5,26] Adding to the evidence for a genetic role in TAD, especially in BAV, tricuspid aortic valve (TAV) first-degree relatives of a BAV patient may have a higher rate of TAD and lower aortic distensibility than the population average but this observation is in question.[27,28] Histologic abnormalities including medial degeneration and elastin fragmentation have been described in both the non-dilated and dilated ascending aorta of BAV patients, implying a common mechanism of TAD.[29] Other clinical observations that less-rigorously reinforce a genetic contribution to TAD in BAV are the occurrence of TAD in BAV patients without significant aortic stenosis especially at young age,[30] or following aortic valve replacement,[31] that average aortic size is greater in patients with BAV than TAV, even after controlling for hemodynamic effects of valvular defects[32] and finally, the severity and prevalence of aortopathy in patients with BAV is greater than what would be expected based on severity of aortic stenosis or regurgitation alone.[17,29]

A normally functioning bicuspid valve causes abnormal and unequal wall stress in the ascending aorta

4D magnetic resonance imaging of the normal TAV shows blood to the ascending aorta with a moderate helical flow in line with the axis of the aorta and with low wall shear stress.[33] Asymmetric opening of the BAV leads to turbulent, non-axial flow in the ascending aorta with a majority of BAV patients having markedly-increased right handed helical flow.[34] This results in increased an unequal wall stress on the ascending aorta[34,35] and sometimes, to asymmetric dilation of the aortic root and ascending aorta.[36-39] Leaflet fusion sub-type is associated with dilatation pattern of the aorta - patients with right-left cusp fusion had larger aortic root diam-

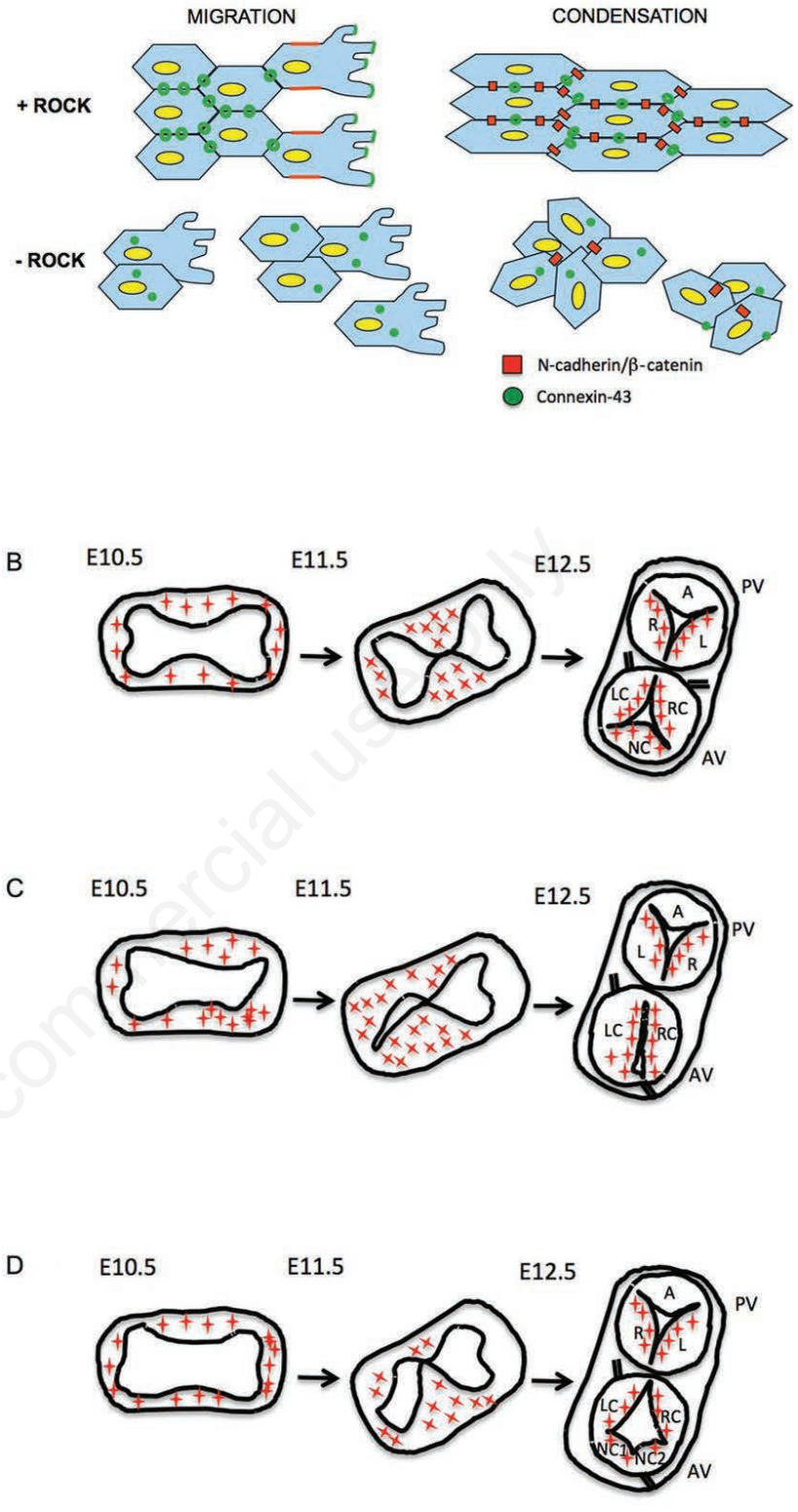

Figure 1. Model for abnormal aortic and pulmonary valve patterning in the developing embryo. A) Abnormalities in cardiac neural crest (CNC) cell adhesion and/or signaling results in disrupted CNC condensation in the outflow cushions. B) Distribution of CNC (red stars) in the outflow tract in normal embryos as the outflow tract septates and tricuspid aortic and pulmonary valves are formed. C and D) CNC do not condense normally in mutant embryos. As a consequence the valve leaflets are abnormally positioned and irregularly sized yielding a bicuspid aortic phenotype (C) or a quadricuspid phenotype (D). From Philips HM *et al.* Cardiovasc Res 2013;99:452-60 (Open Access).

eter and were younger when presenting for surgical interventions than those with right-non-coronary fusion.[39,40]

Responses to abnormal aortic wall stress are not the same in bicuspid and tricuspid aortic valve patients

There are conflicting data on the aortic wall responses to abnormal wall stress in bicuspid and tricuspid aortic valve patients. There are both methodological and interpretative issues that drive the issue. But lets establish a few points over which there is little controversy.

The response of the ascending aorta to increased wall stress has different cellular mechanisms for BAV and TAV patients. In BAV-associated TAD, smooth muscle apoptosis appears to be the dominant histologic event. In contrast, TAV-associated TAD is characterized by elastic fragmentation, cystic medial necrosis and fibrosis, and inflammation.[41] These observations are not confined to the aorta - they are also seen in pulmonary artery of BAV patients, emphasizing the importance of the common aortopulmonary trunk in embryogenesis.[42] Complicating this are differences in the patterns of extracellular matrix proteins seen between the concave and convex surfaces of the ascending aorta of BAV patients.[43]

When the BAV is replaced, without aortic replacement, reducing aortic wall stress, the *average* rate of aortic wall dilation returns to low levels seen in TAV patients.[44,45] This is not surprising as the aortic response to lower wall stress is likely to be reduced after aortic valve replacement (AVR) and the average rate should be fairly similar. But we are not treating average patients; rather it is the outliers that count. Common genetic variants likely have some effect on the average rate of aortic dilation but when aortic wall stress is reduced the impact of these common variants is likely to be small. We can prudently hypothesize that some patients with a burden of common and rare variants that cause aortic dilation will proceed with aortic dilation above the average rate and may require later aortic replacement or repair. This hypothesis is important as it may direct management of the patient presenting for AVR with a moderately dilated aorta. But this hypothesis needs to be proven; which can only be done with sufficiently well-powered and well-phenotyped cohorts with collected DNA, aortic valve and aortic tissues. Indeed, in the absence of these data we can say that the only predictors of rapid aortic dilation are young age, male gender, the aortic root phenotype including the *conjoint cusp opening angle*, *i.e.* alignment of the fused cusp to the aortic axis and right-left BAV configuration.[46-48]

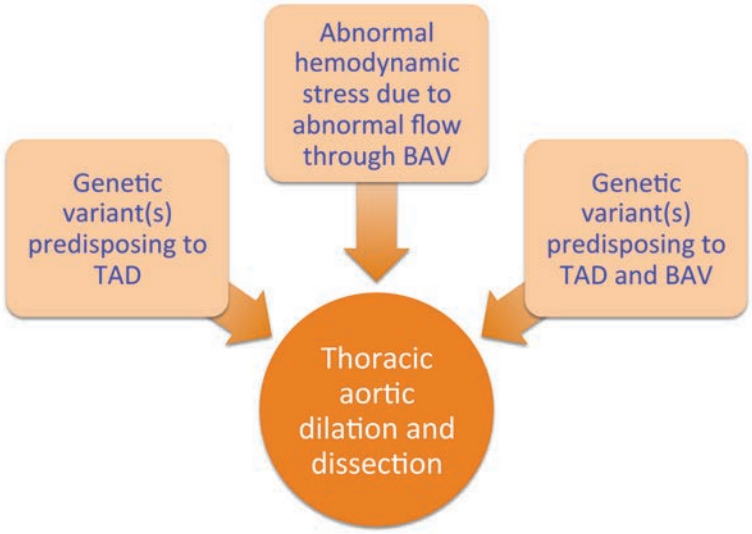

Figure 2. A hypothesis of interacting genetic and hemodynamic causes of bicuspid aortic valve (BAV)-associated thoracic aortic disease (TAD). Common and rare genetic mutations cause BAV and TAD that predispose to TAD in the presence of normal and abnormal hemodynamic stresses from the BAV. Combinations of genetic mutation, BAV configuration and aortic wall shear stress yield different TAD phenotypes between individuals.

How abnormal aortic wall stress and an abnormal aorta interact to cause thoracic aortic disease

While cardiovascular risk factors and older age contribute to TAD, genetic variants in *FBN1*, *ACTA2, FLNA, MYH11, SMAD3, and TGFBR1/2* are also associated with TAD in non-BAV patients. Thus far, only common variants in *FBN1* have been associated with TAD in BAV and reduced fibrillin-1 protein is seen even in patients with normal BAV function.[49] There is marked phenotypic variability in wall stress and TAD even amongst patients with specific BAV fusion pattern and similar levels of valve dysfunction.[50] It is reasonable to believe that varying genetic and non-genetic characteristics between individuals contribute to the level of TAD seen in each individual. Studying these pathological flow patterns and combining it with protein expression and genetic risk profiles could lead to more optimal risk assessment and treatment guidelines. However, despite progress in understanding the varied contributing etiologies in BAV-associated TAD, we still do not fully understand how these factors interact to accurately predict the progression of TAD development or phenotypic expression of TAD.

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